Cancer Mortality in U. S. Counties with Chemical Industries

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Geographic analysis of U. S. cancer mortality, 1950–1969, revealed excess rates for bladder, lung, liver, and certain other cancers among males in 139 counties where the chemical industry is most highly concentrated. The correlation could not be explained by confounding variables such as urbanization, socioeconomic class, or employment in nonchemical industries. If the excess cancer mortality in these areas is due to industrial exposures, the actual risk of cancer among certain chemical workers must be very high. The correlation was limited to counties associated with specific categories of the chemical industry; many involve known occupational hazards, while others suggest new leads to chemically induced cancer in man.

Recent attempts have been made by U. S. governmental agencies to regulate exposure to carcinogens in the chemical manufacturing industry (Stender, 1973). The first list of 14 designated carcinogens has been challenged on the grounds that it may contain agents not carcinogenic for man, and that it omits agents that probably are (Industrial Health Foundation, 1973). The problem is complicated greatly by the insufficient information available on cancer risks among chemical workers. In an indirect but systematic effort to assemble information on cancer hazards associated with the chemical industry, a study was made of cancer mortality statistics for counties of the U. S. that have the highest concentration of chemical workers.

METHODS

The number of manufacturing units engaged in chemical production and the number of employees in these units were available by county from the 1963 Census of Manufacturing, conducted by the U. S. Bureau of the Census (1966). The number of employees for each unit was reported by groups (1–19, 20–49, 50–99, 100–249, 250–499, 500–999, and 1000+). The total number of workers per county was estimated by multiplying the appropriate number of units by the midvalue of each group and then summing the totals. For the last group of employees (1000+), the figure 1500 was used for estimation. The percent of the county population employed in the chemical industry was calculated by dividing the estimated number of employees by the total population of the county in 1963. The counties were then ranked by the magnitude of this percentage and the top 10% of those counties reporting any chemical industry at all (139 counties) were chosen as the study population of chemical-industry counties (CIC).

Cancer mortality rates (average annual, per 100,000 population) were calculated by age, sex, and race for each county of the contiguous United States, 1950–1969 (Mason and McKay, 1973). Using the sixth revision of the International Classification of Diseases (ICD), 35 cancer sites were analyzed by the county of usual residence of the decedent. Age-standardized rates were computed by the direct method, using the total U. S. population in 1960 as the standard (U. S. Bureau of the Census, 1963). The rates for the CIC and various subdivisions were compared with rates for the total U. S. Statistically significant differences resulted when one rate ± its 95% confidence interval did not overlap the other rate ± its interval. Confidence intervals for age-standardized rates were calculated using the standard error estimated according to the method of Chiang (1961).

Detailed analyses of certain cancer sites (lung, liver, and bladder) were conducted when an a priori suspicion of chemically induced cancer was confirmed by our initial analysis. As Table 1 shows, the 139 CIC were divided into three groups (high, intermediate, and low) for lung and bladder cancers, based on the magnitude of the 20-year death rate for each site. In the ICD code, liver cancer could not be distinguished from biliary tract neoplasms until 1958; therefore, the criteria for grouping counties utilized both the more stable 20-year rate (liver and biliary tract) and the more specific 10-year rate (primary liver and intrahepatic bile duct). The "low" category consisted of counties whose age-adjusted mortality rate was equal to or lower than the total U. S. rate. The dividing point for

TABLE 1

Levels of Age-Adjusted Average Annual Mortality (per 10⁵) among White Males

Used to Allocate Individual Counties to a High, Intermediate, or

Low Group for Three Sites of Cancer

		Sites	
Group	Lung	Bladder	Liver ^a
High ^b	≥47.0	≥8.5	10-year rate ≥2.6
Intermediate	39.0-46.9	6.9-8.4	20-year rate ≥ 5.3 10-year rate 1.4–2.5
Low	<39.0	< 6.9	20-year rate ≥ 5.3 10-year rate ≤ 1.4
			20-year rate < 5.3

^a The 20-year death rate (1950–1969) covers malignancies of the liver specified as primary, bile duct or gallbladder specified as primary, and liver primary unspecified. The 10-year rate (1958–1967) is the period when primary liver and intrahepatic bile duct cancers were separated from the others.

b Counties falling into the high group for each site are as follows.

Lung: Dixie, Fla.; Glynn, Ga.; Cherokee, Kans.; Ascension, La.; Calcasieu, La.; Plaquemines, La.; St. Charles, La.; Jasper, Mo.; St. Louis City, Mo.: Middlesex, N.J.; Lenoir, N.C.; Hamilton, Ohio,; Glaveston, Tex.; Jefferson, Tex.; Orange, Tex.; Chesterfield County Combine, Va.

Bladder: Clinton, Iowa, Iberville, La.; Plaquemines, La.; St. James, La.; Yazoo, Miss.; St. Louis City, Mo.; Gloucester, N.J.; Passaic, N.J.; Salem, N.J.; Union, N.J.; Rockland, N.Y.; Warren, N.Y.; Hamilton, Ohio; Galveston. Tex.

Liver: Talladega, Ala.; Dolores, Col.; Power, Id.: Calcasieu, La.; Yazoo, Miss.; Jasper, Mo.; Hamilton, Ohio; Brazoria, Tex.; Harrison, Tex.; Jefferson, Tex.; Orange, Tex.

"high" and "intermediate" rates was arbitrarily chosen to achieve adequate numbers for evaluation in each group. The risk groups for bladder and lung cancers included all 139 counties. For liver cancer, however, 51 counties were excluded from detailed analyses because the selection criteria were not satisfied (e.g., a high 10-year rate for liver cancer, but a low 20-year rate for hepatobiliary cancer).

RESULTS

The estimated number of chemical workers in the CIC was 252,710. This figure compares favorably with the 269,743 workers (7.2% of all employed) identified in these counties by the 1960 Census of the Population (1963). For the entire country in 1960, the number of chemical workers was 864,542 (1.3% of all employed).

Geographic Correlation

Table 2 gives average annual age-adjusted cancer mortality rates for 1950–1969 among white males and females in the CIC and in the total U. S. Rates are presented for all cancers (ICDs 140–205) and four sites which have been linked in previous studies to industrial chemical exposures—lung (ICDs 162 and 163), bladder (ICD 181), liver and biliary passages (ICDs 155 and 156A), and leukemia (ICD 204). In both sexes, the death rates for all cancers were slightly but significantly higher in the CIC. The excess among men in these counties was greater than in women, and could be attributed in part to three of the four cancer sites—lung, bladder, and hepatobiliary system. A breakdown of the hepatobiliary category in 1958–1967 revealed a 10% increase of primary liver cancer in the CIC, with no difference in the rate for gallbladder cancer compared to the total U. S. There was no significant geographic difference for leukemia in children or in adults.

TABLE 2

Average Annual Age-Adjusted Mortality Rafes among Whites for All Malignancies and for Cancers of Four Specific Sites in the Total U.S. and in 139 Chemical-Industry Counties (1950–1969)

				Sites	
	All malignant neoplasms	Lung	Bladder	Liver and gallbladder	Leukemia
Men					
Chemical-industry counties	179.81	41.79	7.19	5.62	8.55
Total U.S.	174.04	37.98	6.78	5.16	8.81
Ratio of rates	1.0	1.1	1.1	1.1	1.0
Difference between rates	5.77*	3.81*	0.41*	0.46*	-0.26
Women					
Chemical-industry counties	131.62	6.45	2.57	5.58	5.60
Total U.S.	130.10	6.29	2.39	5.34	5.74
Ratio of rates	1.0	1.0	1.1	1.0	1.0
Difference between rates	1.52*	0.16	0.18*	0.24*	-0.14

^{*} P < 0.05.

TABLE 3
Measures of Urbanization and Socioeconomic Class for the Total U.S.
AND FOR 139 CHEMICAL-INDUSTRY COUNTIES (1960)

			Socioeconomic level	
	Percent urban ^a	Median school years ^b	Median family income (\$)	Percent unemployed ^c
Chemical-industry counties Total U.S.	70.2 69.9	10.2 10.6	5741 5660	5.1 5.1

- ^a Percent of the population living in urban areas (1960 census definition).
- ^b Median number of years of schooling completed by the adult population 25 years old and older.
- ^c Percent of the civilian labor force that was unemployed.

Among women in the CIC, there was a slightly increased mortality from hepatobiliary cancer, but in 1958–1967 the rates for primary liver cancer and primary biliary tract cancer were identical to those in the total U. S. Women had the same relative excess mortality from bladder cancer (10%) as did men, but the excess in absolute terms was much smaller. No significant geographic differences were found for lung cancer or leukemia among women.

Other Variables

To evaluate the influence of confounding variables, we analyzed county-specific data on urbanization, socioeconomic class (Table 3), and employment in other manufacturing industries (Table 4). The values for the CIC and the total U. S. were remarkably similar. Further evaluation of urbanization was made by using the county data to compare the cancer mortality rates for large metropolitan areas heavily involved in the chemical industry, with rates for similar urban areas not so involved. In 1960, 51 cities in the contiguous United States had a population over 250,000 (U. S. Bureau of the Census, 1963). Three of these cities (Cincinnati, St. Louis, Newark) were represented in the CIC. As shown in Table 5, cancer mortality rates among white males in these three combined areas were consistently higher than the corresponding rates in the areas containing the 48 large cities outside the CIC.

Another check on the comparability of the population in the CIC with the national population, was provided by an analysis of cancers (prostate and breast) unlikely to have a significant occupational component to etiology. In the white population of these counties, the death rates for prostate and breast cancers (17.6 and 25.5, respectively) were virtually identical to the corresponding U. S. rates (17.8, 25.5).

Type of Chemical Industry

The 139 CIC were divided into three groups based on the magnitude of the mortality rate by cancer site. This classification served as the basis for comparing the percent distribution of chemical workers in the manufacturing of specific chemical products (Table 6).

Bladder cancer showed strong positive gradients associated with the manufac-

TABLE 4
PERCENT OF THE WORKING POPULATION EMPLOYED IN NONCHEMICAL MANUFACTURING INDUSTRIES IN THE TOTAL U.S. AND IN 139 CHEMICAL-INDUSTRY COUNTIES, 1960

Other nondurable goods	4.2 2.7
Printing and publishing	1.7
Apparel and other fabricated textiles	1.6
Textile mill products	1.9
Food and kindred products	2.8 2.8
Other durable goods	2.2
Transportation equipment except motor vehicles	1.3
Motor vehicles	1.1
Electrical	2.2
Machinery, except electrical	2.0
Fabricated metal	1.9
Primary metal	1.6
Furniture, lumber and wood products	1.4
	Chemical-industry counties Total U.S.

TABLE 5

Average Annual Age-Adjusted Cancer Mortality Rates (per 10⁵ per Year) among White Males for the Combined Counties Containing the Three Large Cities (>250,000 Population) in the Study Group and Those Containing the Other 48 Cities of This Size within the Contiguous U.S. (1950–1969)

		Sit	es
Counties containing large cities	Lung	Bladder	Liver and gallbladder
Chemical-industry	49.2	9.2	7.2
Others in U.S.	45.1	8.0	5.8

turing of dyes, dye intermediates, and organic pigments; pharmaceutical preparations; and perfumes, cosmetics and other toilet preparations. There were less impressive gradients with industrial gases, soaps and detergents, paints, glue and gelatin, and "chemicals not elsewhere classified." A relation was suggested with printing ink, but the numbers involved are small.

For lung cancer, positive gradients were associated with the manufacturing of industrial gases, pharmaceutical preparations, soaps and detergents, paints, inorganic pigments, and synthetic rubber. Liver cancer yielded positive gradients with the categories "other organic chemicals," synthetic rubber, soaps and detergents, cosmetics and other toilet preparations, and printing ink.

Only one study-group county (Hamilton, Ohio) had a high rate for all three sites. Exclusion of this county from analysis produced the following: (a) diminution of the gradients for bladder and lung cancers with the category of soaps and detergents, (b) loss of the gradient for bladder cancer with "chemicals not elsewhere classified," and (c) loss of the gradients for liver cancer with the categories of soaps and detergents, cosmetics, and printing inks.

Time Trends and Age Patterns

The CIC with high levels of lung, bladder, and liver cancers were used to investigate temporal and age patterns among men. The trends for liver cancer were based on the 1950–1969 rates for all hepatobiliary neoplasms while the age-specific rates were limited to the 1958–1967 data for primary liver cancer.

The high risk CIC had trends similar to those of the entire U. S.: mortality declined for bladder and hepatobiliary cancers and increased for lung cancer (Table 7). The relative excess mortality from cancers of the lung (40%) and hepatobiliary system (30%) in these counties did not change with time, but the relative excess of bladder cancer fell from 50 to 30%.

As shown by Fig. 1, the excess mortality in high-risk counties appeared about age 35–39 for lung cancer, age 45–49 for liver cancer, and age 50–54 for bladder cancer.

Other Cancers

Thirty other cancer sites were inspected for any peculiarities of risk in the CIC. To minimize differences that develop by chance when multiple comparisons are made, we looked for variations that were statistically significant

TABLE 6
NUMBER AND PERCENT DISTRIBUTION OF CHEMICAL WORKERS BY SPECIFIC TYPE OF CHEMICAL MANUFACTURED,^a in Three Groups of Chemical-Industry Counties^b Defined by the Magnitude of the Mortality Rate for Three Sites of Cancer

			Indu	Industrial inorganic and organic chemicals	l organic chem	icals		Plast synti	tic materials ar hetic rubber, s nan-made fiber	Plastic materials and synthetic resins, synthetic rubber, synthetic and other man-made fibers, except glass	sins, ther		Drugs	
Site		Alkalies and chlorine	Industrial gases	Dyes, dye intermediates, and coal tar crudes	Inorganic pigments	Industrial organic chem.,	Industrial inorganic chem., NEC	Plastics materials, synthetic resins	Synthetic	Cellulosic man-made fibers	Synthetic organic fibers	Biological products	Medicinal chemicals	Pharma- ceutical prepa- rations
Bladder	High	0.1	9.6	10.6	1.7	15.6	9.5	5.0	1 4.	2.5	6.2	0.0	2.9	15.0
	Low	5.0	0.3	2.0	0.7	17.9	16.3	9.6	2.8	15.2	8.5	0.3	1.2	4.6
	High	2.6	0.7	4.4	2.9	19.0	12.2	7.2	4.1	1	8.0	0.0	0.1	10.6
Lung	Intermediate	4.9	0.4	7.8	2.0	20.9	12.8	9.8	3.0	6.1	l	0.1	1.6	8.4
	Low	2.1	0.3	1.0	8.0	8.1	21.4	10.1	1.0	17.8	11.2	6.0	1.8	5.9
	High	4.9	9.0	3.9	9.0	26.3	12.8	4.9	6.8	4.9	1	ì	l	3.5
Liver	Intermediate	0.2	9.0	6.9	3.4	14.0	25.2	7.4	3.3	I	I	1	0.2	11.8
	Low	4.7	0.3	2.0	6.0	13.4	14.8	13.8	1.3	18.5	5.5	9.0	6.1	7.1

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Soap, detergents and cleaning preparations, perfumes, cosmetics, and other toilet preparations

	900 d	Joap, uctergents and cleaning preparations, perfumes, cosmetics, and other toilet preparations	and clear perfumes, other toil tions	ung et			Aoric	A oricultural chemicals	i sala		Miscellaneous chemical products	us chemic	a product	و		Percent of
							11Sv.	contain circu	ucais		National Parket		in the second	?		the working
	soap and other detergents	Specialty Surface cleaning, active polishing agents		Perfumes, cosmetics	Paints, varnishes, lacquers	Gum and wood chemicals	Fertilizers	Fertilizers (mixing only)	Fertilizers Agricultural (mixing chem., only) NEC	Glue and gelatin	Glue and gelatin Explosives	Printing ink	Carbon black	Printing Carbon Chemicals, ink black	of chemical in workers	of employed chemical in chemical workers industry
High	7.4	2.9	0.5	12.5	5,4	0.0	1.1	0.2	0.3	1.7	1.3	2.6	ı	3.1	58465	8.4
Bladder Intermediate	2.8	0.1	9.0	3.9	3.9	0.2	1.2	0.7	1.2	0.4	3.1	ł	1.5	2.6	06909	6.7
Low	1.2	0.3	0.0	0.2	9.0	1.7	3.8	8.0	1.0	0.3	3.2	0.2	0.5	1.6	133555	8 .
High	5.8	1.9	0.1	5.1	9.9	1.3	4:4	9.4	0.3	0.5	8.0	6.0	0.2	1.9	65635	5.2
Intermediate	2.3	0.7	0.7	6.5	1.2	1.0	3.1	0.5	-:	1.0	2.3	1.0	9.0	1.4	98605	6.5
Low	l	2.0	0.0	0.3	1.2	1.2	4.1	8.0	1.0	0.5	4.7	0.2	1.0	3.3	88470	9.1
High	8.7	0.7	0.1	4.4	3.2	0.1	3.7	0.4	0.1	0.4	1.9	1.3	0.4	3.3	30460	5.3
Intermediate	2.6	6.4	1.0	2.9	4.0	0.0	9.0	0.1	1.5	0.4	4.0	0.4	1.2	6.1	38230	8.4
Low	1.8	0.4	0 0	1.5	_	1.4	1 3	0.5	0 3	0 3	4.0	0.0	,	7.7	87005	33

^a The categories of chemical manufacturers (titles abbreviated here) are those of the Standard Industrial Classification (SIC) scheme used by the U.S. Bureau of the Census (1963).
^b See methods and Table I for criteria used to allocate counties in three groups.

TABLE 7

AVERAGE ANNUAL AGE-ADJUSTED MORTALITY RATES BY FIVE-YEAR TIME INTERVALS FOR THREE SITES OF CANCER IN THE TOTAL U.S. AND IN SUBGROUPS OF CHEMICAL-INDUSTRY COUNTIES WHICH HAD A HIGH RATE^a FOR A PARTICULAR SITE

			Time	period	
Site		1950–1954	1955-1959	1960-1964	1965-1969
	High counties	33.90	46.09	55.21	67.20
Lung	Total U.S.	25.01	33.25	40.58	49.70
· ·	Risk ratio	1.4	1.4	1.4	1.4
	High counties	10.67	9.86	9.02	8.65
Bladder	Total U.S.	6.94	6.92	6.67	6.62
	Risk ratio	1.5	1.4	1.4	1.3
II aan da ballaana	High counties	8.19	7.35	6.68	5.32
Hepatobiliary	Total U.S.	6.17	5.52	5.08	4.18
•	Risk ratio	1.3	1.3	1.3	1.3

^a See Table 1 for definitions of high chemical-industry counties.

(P < .05) and at least 10% from the U. S. norm. White men in CIC showed 10% elevations in mortality from cancers of the nasal sinuses (ICD 160), larynx (ICD 161), skin (ICD 191), bone (ICD 196), and malignant melanoma (ICD 190). There were 20% increases for mouth and throat cancers (ICDs 141, 143–145, 148) and "other endocrine" malignancies (ICD 195). In white women, 10% excesses in mortality were noted for cancers of the nasopharynx (ICD 146), uterine cervix (ICD 171), other uterus (ICDs 172–174), and malignant melanoma. There was a 20% excess of deaths from cancers of the nasal sinuses.

The death rates for nasopharyngeal and nasal-sinus cancers in men and women residents of the CIC were significantly higher than the corresponding rates in the total U. S., and were elevated at least 10% in every instance except for nasopharyngeal cancer among men (risk ratio = 1.03). Among those individual counties with high mortality from nasopharyngeal cancer, the rate for

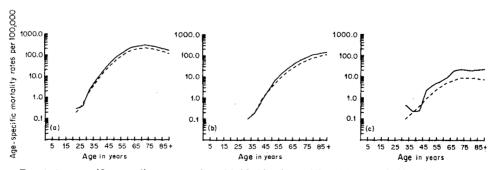


FIG. 1. Age-specific mortality rates per lung (a), bladder (b), and liver (c) cancer in high risk chemical-industry counties (CIC) ____ and in the total U. S. ____. (See Table 1 for definition of "high-risk" counties for each tumor type.)

bladder cancernalso tended to be high. Thus, within the CIC, the correlation coefficient for the nasopharyngeal and bladder cancer rates was 0.19 in men and 0.18 in women. In contrast, coefficients of -0.02 and -0.01 were calculated from corresponding data based on all 3056 counties within the contiguous U. S.

Stomach cancer was the only neoplasm among white males with significantly low mortality in the CIC (14.22) compared to the total U. S. (15.22). White females in the CIC also demonstrated a deficit (7.17 vs 7.70). These differences could not be attributed to urbanization or social class differences.

Nonwhites

Nonwhites comprised only 13.5% of the population of the CIC in 1960 (U. S. Bureau of the Census, 1963). The findings in this group, while less stable because of the smaller numbers, are generally similar to those for whites. Nonwhite men in these counties showed 10% higher mortality from all cancers, and from cancers of the lung and bladder, as compared to the U. S. nonwhite population. There was no increase in hepatobiliary malignancies. Nonwhites showed similar elevations to those among whites for other cancers, except for cancers of the nasopharynx, nasal sinuses, and malignant melanoma. The stomach cancer rates in nonwhite men and women were similar to those in the total U. S.

DISCUSSION

There are many limitations to the epidemiologic technique of geographic correlation between disease and suspected etiologic variables. Because of the dilutional effect imposed by studying aggregates of people, mostly unexposed to the suspected agents, the estimated cancer risk in the chemical-industry areas should be much lower than the actual risk to chemical workers. If the 10% excesses of bladder, lung and hepatobiliary cancers among men in the chemical-industry counties are due to occupational exposures (by the 7.2% of the employed population who work in the chemical industry), the risk of these cancers in chemical workers would be about two to three times that of the general population. Since cancer mortality was not elevated in all chemical-industry counties, the excess risk may apply to only a portion of all chemical plants, and probably to only a portion of workers in these plants. Thus, the relatively small increases in site-specific cancer mortality in these analyses may reflect large excesses of risk among workers exposed to hazardous processes.

Another limitation of this type of study is that the geographic correlation may be due to a mutual association with another variable. However, socioeconomic class, urbanization, and other manufacturing processes could not account for the correlations observed in this study, though it is possible that other confounding variables may be involved. Of particular concern is cigarette smoking, which is associated with cancers of the lung, bladder, and other sites (Hammond, 1966). If smoking were more prominent in the CIC, one would expect lung cancer excesses in both men and women residents. The restriction of the excess lung cancer risk to men in this study suggests an occupational factor, as does the male-limited excess of liver cancer. Although not limited to males, the excess of

bladder cancer deaths in CIC was associated with the production of dyes and dye intermediates, pharmaceutical preparations, paints, and printing inks. These correlations are compatible with the high risk of bladder cancer reported in workers exposed to β -naphthylamine, benzidine (Case *et al.*, 1954), paints (Wynder *et al.*, 1963; Cole *et al.*, 1972) and printing inks (H. M. Chief Inspector of Factories, 1965). The decline over time in the relative excess of bladder cancer in the CIC probably reflects the discontinued production of β -naphthylamine and the safety measures introduced in producing benzidine in the early 1950s.

This study yielded other clues to occupational carcinogenesis, such as the elevated mortality from cancers of the nasopharynx and nasal sinus in the CIC. In these areas, but not in the total U. S., the rates for nasopharyngeal cancer correlated with those for bladder cancer. This relationship is consistent with evidence that workers in the finishing rooms of leather and shoe factories are prone to nasal and bladder cancers (Acheson et al., 1970; Cole et al., 1972) suggesting that chemicals may be carcinogenic at the sites of adsorption and excretion (Cole et al., 1972). The increased risk of bladder and nasal tumors among males and females in the CIC raises the possibility that occupational carcinogens may have escaped into the general environment.

Also, recent reports of liver angiosarcoma among workers exposed to vinyl chloride (Creech and Johnson, 1974; Lee and Harry, 1974) strengthen the possibility that occupational chemicals may have produced the elevated risk of liver cancer in the CIC, particularly the areas concerned with synthetic rubber manufacturing. The data available to us on liver cancer cannot be analyzed by cell type, but suggest that occupational determinants of this tumor may be more important than previously believed.

In addition, this study suggests some fresh leads to chemical exposures that may be carcinogenic. Of particular note are the elevated rates of (1) bladder cancer in counties manufacturing cosmetics, industrial gases, and soaps and detergents; (2) lung cancer in counties producing pharmaceutical preparations, soaps and detergents, paints, inorganic pigments, and synthetic rubber; and (3) liver cancer in counties manufacturing cosmetics, soaps and detergents, and printing inks.

These findings indicate the need for further analytic studies of cancer risk in industrial groups, and point to locations where investigations might be most productive. With the cooperation of industry, labor and independent investigators, such studies should be able to clarify the risk of cancer in various groups of chemical workers, assess the influence of other risk factors, identify the hazardous processes, and evaluate the effects of safety measures.

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